2001-441716/47 B04 D16 EXIQ- 1999.12.23
EXIQON AS *WO 200148190-A2
1999.12.23 1999-171873(+1999US-171873) *(2001.07.05)* C12N 15/11, A61K 31/712, C07H 21/00 // A61P 29/00, 35/00

Use of LNA-modified oligonucleotide for modulating expression of genes involved in malignant cell growth, tumor suppression, DNA repair, and for treating malignant cell growth and inflammatory disease/disorder (Eng)

C2001-133465 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW)

Addnl. Data: ORUM H, KOCH T, SKOUV J, JAKOBSEN M H
2000.12.22 2000WO-IB02043

B(4-E1, 4-E6, 4-F1E, 4-F2E, 4-N2, 4-N2E, 11-C8E1, 12-M5, 14-C3, 14-C9, 14-G2, 14-G2A, 14-G3, 14-H1, 14-J1, 14-L6, 14-N1, 14-S3) D(5-C7, 5-H8, 5-H12, 5-H12D2, 5-H14, 5-H14B2, 5-H17, 5-H18, 5-H19) .15

methylene bridge) for modulating gene expression involved in malignant cell growth, tumor suppression, DNA repair, oncogene, gene encoding multidrug transporter protein, signal transduction pathway gene for regulating cell growth, gene associated with inflammatory disease, and treating malignant cell growth and inflammatory disorder.

DETAILED DESCRIPTION

Use of LNA-modified oligonucleotide (comprising 2'-O, 4'-C-methylene bridge) for modulating expression of genes involved in malignant cell growth, tumor suppression, DNA repair, oncogene, gene encoding multidrug transporter protein, signal transduction pathway gene for regulating cell growth, gene associated with inflammatory disease, and treating malignant cell growth and inflammatory disease/disorder. The gene or RNA from the gene is contacted with the LNA-modified oligonucleotide (I). (I) is administered to a mammal suffering from or susceptible from

NOVELTY

Using LNA-modified oligonucleotide (comprising 2'-O, 4'-C-methylene bridge) for modulating gene expression involved in malignant cell growth and inflammatory disease/disorder.

ACTIVITY

Antiinflammatory; cytostatic; antitumor; antiarthritic; osteopathic; antiallergic; immunosuppressive; neuroprotective.

MECHANISM OF ACTION

Modulator of gene expression (claimed); antisense therapy.
No supporting data is given.

USE

(I) is useful for modulating expression of genes involved in malignant cell growth, tumor suppression, DNA repair, oncogene, gene encoding multidrug transporter protein, signal transduction pathway gene for regulating cell growth, and gene associated with inflammatory disease. (I) is useful for treating inflammatory disease or disorder, and malignant cell growth comprising a solid tumor or a leukemic malignancy in a mammal, where the malignant cell growth is present in lung, liver, stomach, intestine, bowel, prostate, brain, testes or ovaries of the mammal. The mammal suffers from undesired expression of an oncogene, a tumor suppressor gene, a DNA repair gene, an MMP gene, a gene encoding a multidrug transporter protein, or a gene involved in the signal transduction pathway regulating cell growth (claimed).
(I) is useful for treating disease and disorders associated with inflammation, such as arthritic conditions, osteoarthritis, multiple sclerosis, allergic conditions and other autoimmune conditions.

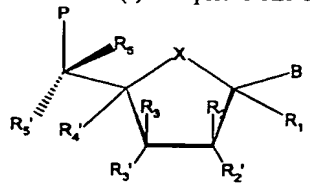
ADMINISTRATION

(I) is administered by oral, topical, intravenous or subcutaneous route.
No dosage details are given.

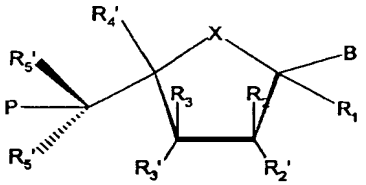
TECHNOLOGY FOCUS

Biotechnology - Preferred Method: Contacting gene with (I) results in inhibition of expression of the gene. The gene comprises at least a portion of a sequence given in the specification, and (I) hybridizes with messenger RNA of the gene or sequence to inhibit its expression. The gene associated with inflammatory disease comprises a CD marker gene, a gene encoding an adhesion molecule, a gene encoding a chemokine or chemokine receptor, a gene encoding interleukin or interleukin receptor or a gene encoding an immunoglobulin, an immunoglobulin receptor, or a subunit of the immunoglobulin. The

gene associated with inflammatory disease comprises a gene encoding immunoglobulin (Ig)E, FcεRIα, IgG, IgA1, IgA2, IgM, IgD, a gene encoding their corresponding receptors or a gene encoding their subunits. (I) comprises from about 8-60 base units, preferably 10-40 base units. (I) comprises one or more units of formula (1a) or (1b).



(Ia)



(Ib)

X = O, S or C;
B = nucleobase;
R_1, R_2, R2', R_3, R3', R_5, R5' = H, methyl, ethyl, propyl, propynyl, aminoalkyl, methoxy, propoxy, methoxy-ethoxy, fluoro or chloro;
P = is the radical position for an internucleoside linkage to a proceeding monomer or a 5' terminal group; and
R_3 or R3' = an internucleoside linkage to a proceeding monomer or a 3'-terminal group.
(50pp3277DwgNo.0/3)

[11] **Patent Number: WO0148190**
[45] **Date of Patent: Jul. 05, 2001**

[54] THERAPEUTIC USES OF LNA-MODIFIED OLIGONUCLEOTIDES

[75] Inventor(s): **ORUM; Henrik** Vildrosevej 3, Hareskovby, DK-3500 Vaerlose DK DK DK
KOCH; Troels Funkiavej 47, DK-2300 Copenhagen S DK DK DK
SKOUV; Jan Stokholmsvej 55, DK-3060 Espergaerde DK DK DK
JAKOBSEN; Mogens Havsteen, Vanlose, Alekistevej 225, 1., DK-2720 Vanlose DK DK DK

[21] Appl. No.: **IB0002043 IB**

[22] Filed: **Dec. 22, 2000**
[73] Assignee: **EXIQON A/S; Bygstubben 9** DK-2950 Vedbaek DK DK DK
[30] Foreign Application Priority Data:
US Dec. 23, 1999 60/171873

[51] **Int. Cl.**[6] **A61K031712**
[51] **Int. Cl.**[6] **C07H02100**
[51] **Int. Cl.**[6] **C07H02100**
[51] **Int. Cl.**[6] **C07H02100**
[51] **Int. Cl.**[6] **A61P02900**
[51] **Int. Cl.**[6] **A61P03500** *Attorney, Agent, or Firm -Legal firm* - KRAUS, W.

[57] **ABSTRACT**

The invention relates to therapeutic applications of LNA-modified oligonucleotides. In particular, the invention provides methods for treatment of undesired cell growth as well as treatment of inflammatory related diseases and disorders. Preferably, administration of an LNA- modified oligonucleotide modulates expression of a targeted gene associated with the undesired cell growth or an inflammatory related disease or disorder.

Table 1 below lists a number of genes involved in the establishment, growth, invasion and metastasis of tumors and genes involved in the development of resistance to chemotherapeutic drugs that are particularly interesting as antisense targets. It should be understood that many of the genes listed in table 1 are representatives of a larger gene family the other members of which also constitute potentially important antisense targets, e.g. ADAMTS- I is a member of the ADAMs gene family that encode cellular disintegrins and metalloproteinases, MMP- I is a member of the matrix metalloproteinases (MM?s) gene family that encode zincdependent endoproteinases, etc. Table I

ABL1 COT GL13 PA12 ABL2 CREBI GRO1 PCNA ABR CREBBP GR02 PDGFA ADAM I I CRK GR03 PDGFB ADAMTS-1 CRKL HCK PDGFRA DT3 AKT1 CSFI HGF PDGFRjE) AK12 CSFIR HKR3 PIRI APC CSF2 HOXI I PLAT ARAFI CSF2RA HOXA10 PLAU ARAF2 CSF2RB HOXB2 PLAUR ARHA CSF3R HSPA9 PMSI ARHB DIOS170 HRAS PMS2 ARHC DAP IFNB1 PPARA AT DAP3 IFNG PPARBP AXL DAPKI IFNGRI PPARG BAD DBCCRI IFNGR2 PTCH BAG1 DCC IRF4 PVTI BAII DDX6 JUN RAF1 BAK1 E2FI JUNB RALA BAPI E2F4 JUND RALB BARDI E4FI KAII RARA BAX EGF KIT RARB BCL2 EGFR KRAS2 RARG BCL2AI EIF3S2 LCK

RASAI BCL3 EIF3S6 LCNI RB1 BCL5 EIF4E LCN2 RBBP6 BCL6 EIFE4EBP1 LCO REL BCNS ELE1 LCPI RELA BCR ELK1 LCP2 REQ BCS ELK3 LPSA RET BL ELK4 LTA RMYC BLYM EMPI LTB ROS I BMII EMS1 LTK RRAS BMYC EPHAI LYN SEA BRAF EPHA3 MAD SET BRCAI ERBAL2 MADH4 sis BRCA2 ERBB2 MAF SKI BRCDI ERBB3 MAFG SKIL CALCR ERBB4 MAFK SMARCBI CASPI ERG MAP2K1 spil CASP2 ERPLI MAP2K4 SPINK1 CASP3 ESR1 MAP2K6 SRC CASP4 ESR2 MAP3K7 ST5 CASP5 ESRRA MAP3K8 SUPT3H CASP6 ESRRB MAP3KI4 SUPT51-1 CASP13 ESRRG MAPKAPK3 SUPT614 CBL ETSI MISI TAF2A CCNAI ETS2 M4SI TAF2H CCNA2 ETV3 M6P2 TALI CCNB1 ETV4 MPL TF CCNB2 ETV6 MASI THPO CCNC EVII MAX THRA CCNDI EWSR1 MCC THRB CCND2 FAT MCF2 TIAMI CCND3 FER MDM2 TIM CCNEI FES MDR-1 TIMP-1 CCNE2 FGD1 MDR-2 TIMP-2 CCNF FGFI MEL TM4SF1 CCNGI FGF2 MENI TNF CCNG2 FGF3 MET TP53 CCNH FGF4 MGR-2 TP53BP2 CCNK FGF5 MLHI TP73 CCNTI FGF6 MMP-1 VAV1 CCNT2 FGF7 MMP-2 VAV2 CDC23

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 July 2001 (05.07.2001)

PCT

(10) International Publication Number
WO 01/48190 A2

(51) International Patent Classification[7]: C12N 15/11, A61K 31/712, C07H 21/00 // A61P 29/00, 35/00

(21) International Application Number: PCT/IB00/02043

(22) International Filing Date:
22 December 2000 (22.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/171,873 23 December 1999 (23.12.1999) US

(71) Applicant *(for all designated States except US)*: **EXIQON A/S** [DK/DK]; Bygstubben 9, DK-2950 Vedbaek (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ORUM, Henrik** [DK/DK]; Vildrosejej 3, Hareskovby, DK-3500 Vaerlose (DK). **KOCH, Troel** [DK/DK]; Funkiavej 47, DK-2300 Copenhagen S (DK). **SKOUV, Jan** [DK/DK]; Stokholmsvej 55, DK-3060 Espergade (DK). **JAKOBSEN, Mogen, Havsteen** [DK/DK]; Vanlose, Alekistevej 225, 1., DK-2720 Vanlose (DK).

(74) Agents: **KRAUS, W.** et al.; Thomas-Wimmer-Ring 15, D-80539 München (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/48190 A2

(54) Title: THERAPEUTIC USES OF LNA-MODIFIED OLIGONUCLEOTIDES

(57) Abstract: The invention relates to therapeutic applications of LNA-modified oligonucleotides. In particular, the invention provides methods for treatment of undesired cell growth as well as treatment of inflammatory related diseases and disorders. Preferably, administration of an LNA-modified oligonucleotide modulates expression of a targeted gene associated with the undesired cell growth or an inflammatory related disease or disorder.

The LNA modified antisense oligonucleotide may comprise antisense oligonucleotides specific to any tumour suppressor genes such as TP53, RB1, P16, oncogenes such as RAS and MYC or DNA repair genes such as MSH2 and MLH1 involved in the establishment and growth of a tumour. It may also be targeted against genes which are involved in tumour angiogenesis and metastasis such as for example the genes MMP-1 and MMP-2 which belong to the MMP family of matrix metalloproteinases that degrade connective tissue. Also, The LNA modified oligonucleotides may be directed against genes encoding multidrug transporter proteins such as the genes MDR-1 and MDR-2. Overexpression of such genes leads to multidrug resistance which is a major limitation to the success of current chemotherapy. Also, the LNA modified oligonucleotide may be directed against genes involved in the signal transduction pathway regulating cell growth such as cyclins and cyclin dependent kinases.

Table 1 below lists a number of genes involved in the establishment, growth, invasion and metastasis of tumors and genes involved in the development of resistance to chemotherapeutic drugs that are particularly interesting as antisense targets. It should be understood that many of the genes listed in table 1 are representatives of a larger gene family the other members of which also constitute potentially important antisense targets, e.g. ADAMTS-1 is a member of the ADAMs gene family that encode cellular disintegrins and metalloproteinases, MMP-1 is a member of the matrix metalloproteinases (MMPs) gene family that encode zinc-dependent endoproteinases, etc.

Table 1

ABL1	COT	GLI3	PAI2
ABL2	CREB1	GRO1	PCNA
ABR	CREBBP	GRO2	PDGFA
ADAM11	CRK	GRO3	PDGFB
ADAMTS-1	CRKL	HCK	PDGFRA
AKT1	CSF1	HGF	PDGFRB
AKT2	CSF1R	HKR3	PIM1
APC	CSF2	HOX11	PLAT
ARAF1	CSF2RA	HOXA10	PLAU

ARAF2	CSF2RB	HOXB2	PLAUR
AREG	CSF2RY	HPC1	PLG
ARHA	CSF3R	HSPA9	PMS1
ARHB	D10S170	HRAS	PMS2
ARHC	DAP	IFNB1	PPARA
AT	DAP3	IFNG	PPARBP
AXL	DAPK1	IFNGR1	PPARG
BAD	DBCCR1	IFNGR2	PTCH
BAG1	DCC	IRF4	PVT1
BAI1	DDX6	JUN	RAF1
BAK1	E2F1	JUNB	RALA
BAP1	E2F4	JUND	RALB
BARD1	E4F1	KAI1	RARA
BAX	EGF	KIT	RARB
BCL2	EGFR	KRAS2	RARG
BCL2A1	EIF3S2	LCK	RASA1
BCL3	EIF3S6	LCN1	RB1
BCL5	EIF4E	LCN2	RBBP6
BCL6	EIFE4EBP1	LCO	REL
BCNS	ELE1	LCP1	RELA
BCR	ELK1	LCP2	REQ
BCS	ELK3	LPSA	RET
BL	ELK4	LTA	RMYC
BLYM	EMP1	LTB	ROS1
BMI1	EMS1	LTK	RRAS
BMYC	EPHA1	LYN	SEA
BRAF	EPHA3	MAD	SET
BRCA1	ERBAL2	MADH4	SIS
BRCA2	ERBB2	MAF	SKI
BRCD1	ERBB3	MAFG	SKIL
CALCR	ERBB4	MAFK	SMARCB1
CASP1	ERG	MAP2K1	SPI1
CASP2	ERPL1	MAP2K4	SPINK1
CASP3	ESR1	MAP2K6	SRC
CASP4	ESR2	MAP3K7	ST5
CASP5	ESRRA	MAP3K8	SUPT3H
CASP6	ESRRB	MAP3K14	SUPT5H
CASP13	ESRRG	MAPKAPK3	SUPT6H
CBL	ETS1	M1S1	TAF2A
CCNA1	ETS2	M4S1	TAF2H
CCNA2	ETV3	M6P2	TAL1
CCNB1	ETV4	MPL	TF
CCNB2	ETV6	MAS1	THPO
CCNC	EVI1	MAX	THRA
CCND1	EWSR1	MCC	THRB
CCND2	FAT	MCF2	TIAM1

CCND3	FER	MDM2	TIM
CCNE1	FES	MDR-1	TIMP-1
CCNE2	FGD1	MDR-2	TIMP-2
CCNF	FGF1	MEL	TM4SF1
CCNG1	FGF2	MEN1	TNF
CCNG2	FGF3	MET	TP53
CCNH	FGF4	MGR-2	TP53BP2
CCNK	FGF5	MLH1	TP73
CCNT1	FGF6	MMP-1	VAV1
CCNT2	FGF7	MMP-2	VAV2
CDC23	FGF8	MMP-3	VDR
CDC25A	FGF9	MMP-9	VEGF
CDC25C	FGF10	MNAT1	VGF
CDC2L1	FGF11	MOS	VHL
CDC2L2	FGF12	MPL	WNT1
CDC34	FGF13	MSH2	WNT2
CDH1	FGF14	MYB	WNT5A
CDH5	FGF16	MYBL1	WT1
CDH7	FGF17	MYBL2	YES1
CDK2	FGF18	MYC	
CDK3	FGF19	MYCL1	
CDK4	FGFR1	MYCN	
CDK5	FGFR2	NBL1	
CDK6	FGFR3	NF1	
CDK7	FGFR4	NF2	
CDK8	FGR	NFKB2	
CDK9	FKHL1	NKTR	
CDK10	FLI1	NOS2A	
CDKL1	FLT1	NOS2B	
CDKL2	FMS	NOS2C	
CDKN1A	FPS	NOS3	
CDKN1B	FOS	NOTCH4	
CDKN1C	FOSB	NOV	
CDKN2A	FOSL1	NRAS	
CDKN2B	FOSL2	NRG1	
CDKN2C	FYN	NRG2	
CDKN2D	GADD45A	NTRK1	
CDKN3	GAK	ODC1	
CDL4	GLI	PACE	
CHES1	GLI2	PAI1	

It should be appreciated that in the above table 1, an indicated gene means the gene and all currently known variants thereof, including the different mRNA transcripts that the gene and its variants can give rise to, and any further gene variants

What is claimed is:

1. A method of modulating expression of a gene involved in malignant cell growth, comprising contacting the gene or RNA from the gene with an oligonucleotide that comprises one or more LNA units, whereby gene expression is modulated.

2. The method of claim 1 wherein contact with the LNA oligonucleotide results in inhibition of expression of the gene.

3. A method of modulating expression of an oncogene, tumor suppressor gene, a DNA repair gene, an MMP gene, a gene encoding a multidrug transporter protein, or a gene involved in the signal transduction pathway regulating cell growth, comprising contacting the gene or RNA from the gene with an oligonucleotide that comprises one or more LNA units, whereby gene expression is modulated.

4. The method of claim 3 wherein contact with the LNA oligonucleotide results in inhibition of gene expression.

5. The method of any one of claims 1 through 4 wherein the gene comprises at least a portion of a sequence identified in table 1 above.

6. The method of claim 2 or claim 4 wherein the LNA oligonucleotide hybridizes with messenger RNA of the gene to inhibit expression thereof.

7. A method of treating a mammal suffering from or susceptible from malignant cell growth, comprising:

administering to the mammal an effective amount of an oligonucleotide that comprises one or more LNA units.

8. The method of claim 7 wherein the malignant cell growth comprises a solid tumor or a leukemic malignancy.

9. The method of claim 7 or claim 8 wherein the malignant cell growth is present in a lung, liver, stomach, intestine, bowel, prostate, brain, testes or ovaries of the mammal.

10. The method of any one of claims 7 through 9 wherein the mammal suffers from undesired expression of an oncogene, a tumor suppressor gene, a DNA repair gene, an MMP gene, a gene encoding a multidrug transporter protein, or a gene involved in the signal transduction pathway regulating cell growth.

11. The method of any one of claims 7 through 10 wherein the mammal suffers from undesired expression of at least a portion of a sequence identified in table 1 above.

12. The method of claim 10 or claim 11 wherein the administered LNA oligonucleotide hybridizes with messenger RNA of the gene or sequence to inhibit expression thereof.

13. A method of modulating expression of a gene associated with an inflammatory disease, comprising contacting the gene or RNA from the gene with an oligonucleotide that comprises one or more LNA units, whereby gene expression is modulated.

14. The method of claim 13 wherein contact with the LNA oligonucleotide results in inhibition of gene expression.

15. The method of claim 13 or claim 14 wherein the gene comprises a CD marker gene, a gene encoding an adhesion molecule, a gene encoding a chemokine or chemokine receptor, a gene encoding interleukin or interleukin receptor, or a gene

encoding an immuoglobulin, an immunoglobulin receptor, or a subunit of an immunoglobulin.

16. The method of any one of claims 13, 14 or 15 wherein the gene comprises a gene encoding IgE, FcεRIα, IgG, IgA1, IgA2, IgM, IgD, a gene encoding their corresponding receptors or a gene encoding their subunits.

17. A method of any one of claims 13, 14 or 15 wherein the gene comprises at least a portion of a sequence identified in tables 2, 3, 4 or 5 above.

18. The method of any one of claims 13 through 17 wherein the administered LNA oligonucleotide hybridizes with messenger RNA of the gene or sequence to inhibit expression thereof.

19. A method of treating a mammal suffering from or susceptible from an inflammatory disease or disorder, comprising:

administering to the mammal an effective amount of an oligonucleotide that comprises one or more LNA units.

20. The method of claim 19 wherein the mammal suffers from undesired expression of a CD marker gene, a gene encoding an adhesion molecule, a gene encoding a chemokine or chemokine receptor, a gene encoding interleukin or interleukin receptor, or a gene encoding an immuoglobulin, an immunoglobulin receptor or an immunoglobulin subunit.

21. The method of claim 19 or 20 wherein the mammal suffers from undesired expression of a gene encoding IgE, FcεRIα, IgG, IgA1, IgA2, IgM, IgD a gene encoding their corresponding receptors, or a gene encoding their subunits.

22. A method of any one of claims 19 or 20 wherein the mammal suffers from undesired expression of at least a portion of a sequence identified in tables 2, 3, 4 or 5 above.

L4 ANSWER 2 OF 2 WPIX (C) 2002 THOMSON DERWENT
AN 2001-441716 [47] WPIX Full-text
DNC C2001-133465
TI Use of LNA-modified oligonucleotide for modulating expression of genes involved in malignant cell growth, tumor suppression, DNA repair, and for treating malignant cell growth and inflammatory disease/disorder.
DC B04 D16
IN JAKOBSEN, M H; KOCH, T; ORUM, H; SKOUV, J
PA (EXIQ-N) EXIQON AS; (JAKO-I) JAKOBSEN M H; (KOCH-I) KOCH T; (ORUM-I) ORUM H; (SKOU-I) SKOUV J
CYC 94
PI WO 2001048190 A2 20010705 (200147)* EN 50p <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001030417 A 20010709 (200164)
US 2002068709 A1 20020606 (200241)
ADT WO 2001048190 A2 WO 2000-IB2043 20001222; AU 2001030417 A AU 2001-30417 20001222; US 2002068709 A1 Provisional US 1999-171873P 19991223, US 2000-747913 20001222
FDT AU 2001030417 A Based on WO 200148190
PRAI US 1999-171873P 19991223; US 2000-747913 20001222